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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/809,824	03/25/2004	Simon Albertus Langeveld	2183-6395US	7947

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TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER	
MUMMERT, STEPHANIE KANE	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/809,824	LANGEVELD ET AL.
	Examiner	Art Unit
	Stephanie K. Mummert	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/25/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in Netherlands on September 25, 2001. A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on March 25, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5-6, 15 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 5, the term 'a primer' is vague and indefinite because there are multiple primers with antecedent basis to this claim and it is unclear which of the primers is intended to serve as a sequencing primer.

Regarding claim 6, the term 'said primer' is vague and indefinite because there are multiple primers with antecedent basis to the claim and it is unclear which of the primer is intended to initiate a sequencing reaction.

Regarding claim 15, the term 'close proximity to a short stretch of identical nucleotides' is vague and indefinite. The nucleotides are identical to what – identical to each other or to the hybridizing primer? How are 'close proximity' and 'short stretch' defined?

Regarding claim 17, the term 'close proximity to a short stretch of identical nucleotides' is vague and indefinite. The nucleotides are identical to what – identical to each other or identical to the hybridizing primer? How are the terms 'close proximity' and 'short stretch' defined?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilkinson et al. (1995, Plant Molecular Biology, vol. 27, no. 6, pp. 1097-1108) in view of Kambara (US PgPub, 2003/0124544; July 2003). Wilkinson teaches an examination of fruit ripening in strawberry to analyze genes with differential expression during strawberry fruit ripening).

With regards to claim 1, Wilkinson teaches a method for comprising determining the expression of at least a first gene and a second gene, or a gene fragment, said method comprising:

a) providing at least a first nucleic acid template derived from said first gene and a second nucleic acid template derived from said second gene (p. 1100, col. 1, 'Results' heading, lines 8-16, where about one twelfth of all mRNAs should be present)

b) hybridizing at least one first primer to said first template and at least one second primer to said second template (p. 1099, col. 1, lines 8-20); and

c) determining binding of said primers to said templates in one reaction vessel (Figure 1, where PCR products of PCR differential display experiment).

With regards to claim 2, Wilkinson teaches a method wherein determining binding of said primers to said templates comprises a sequencing step (Figure 1, where the samples are run on a denaturing polyacrylamide gel; and also, p. 1099 col. 2, 'DNA sequence analysis' heading).

With regards to claim 3, Wilkinson teaches a method wherein said sequencing step comprises sequencing amplified DNA (p. 1099 'DNA sequence analysis' heading where amplified cDNA clones were sequenced).

With regards to claim 4, Wilkinson teaches a method wherein said amplified DNA comprises PCR-amplified DNA (see p. 1099, col. 1, lines 8-20, where PCR conditions are taught).

With regards to claim 5, Wilkinson teaches a method wherein said primer comprises a sequencing primer (p. 1099, col. 2, 'DNA sequence analysis' heading, where).

With regards to claim 6, Wilkinson teaches a method wherein said primer can initiate a sequencing reaction carried out by a DNA polymerase (p. 1099, where the sequencing reaction is carried out with a SEQUENASE DNA sequencing kit).

With regards to claim 10, Wilkinson teaches a method, wherein said first gene and said second gene are variably expressed during development (Figures 2 and 3, where different stages of strawberry development and ripening are examined and the expression of multiple differentially expressed genes are analyzed by Northern blot).

With regards to claim 11, Wilkinson teaches a method, wherein said organism comprises a plant (Abstract, where the plant is a soft fruit species, raspberry).

With regards to claim 12, Wilkinson teaches a method, wherein hybridizing at least one first primer to said first template and at least one second primer to said second template is performed in one reaction vessel (p. 1099, col. 1, lines 8-20 and p. 1100, col. 1, lines 14-20, 'results' heading, where PCR products were resolved in a single lane of a denaturing gel, see Figure 1).

With regards to claim 13, Wilkinson teaches a method, wherein providing at least a first nucleic acid template derived from said first gene and a second nucleic acid template derived from said second gene is performed in one reaction vessel (p. 1099, col. 1, lines 8-20 and p. 1100, col. 1, lines 14-20, 'results' heading, where PCR products were resolved in a single lane of a denaturing gel, see Figure 1).

With regards to claim 17, Wilkinson teaches a method, wherein said additional primer is selected to hybridize at least in close proximity to a relative short stretch of identical nucleotides on said second template (Figure 1).

Wilkinson does not teach sequencing using an RNA dependent DNA polymerase or a method that uses a dATP or ddATP analogue, specifically dATPαS. Wilkinson also does not teach the hybridization of multiple primers in close proximity to a short stretch of identical nucleotides. Kambara teaches a method for examining nucleotide sequences of a sample having multiple test sites (Abstract, lines 1-2)

With regards to claim 7, Kambara teaches a method wherein said DNA polymerase is an RNA dependent DNA polymerase (p. 5, paragraph 63, where Taq DNA polymerase is used, and where Taq has RNA-dependent DNA polymerase activity as evidenced by Maudru, et al. Abstract, J. Virol. Methods. 66(2):247-61).

With regards to claim 8, Kambara teaches a method wherein a dATP or ddATP analogue is used which is capable of acting as a substrate for said DNA polymerase, but incapable of acting as a substrate for a pyrophosphate detection enzyme (paragraph 74, where a dATP analogue, dATPαS is used).

With regards to claim 9, Kambara teaches a method wherein said analogue comprises deoxyadenosine thio triphosphate (dATPαS) (paragraph 74, where a dATP analogue, dATPαS is used).

With regards to claim 14, Kambara teaches a method, comprising hybridizing at least one additional primer to said first template (Figure 1, where multiple primers are hybridized to the same template).

With regards to claim 15, Kambara teaches a method, wherein said additional primer is selected to hybridize at least in close proximity to a short stretch of identical nucleotides on said first template (p. 5, col. 2, paragraphs 66-68, as an example where primers 2 or 3 would bind sequence 1 in close proximity in the 5' direction to multiple instances of GG and CCC; where 'short stretch of identical nucleotides is interpreted to mean 2 or more nucleotides of the same type, e.g. CC, AA, TT, GG).

With regards to claim 16, Kambara teaches a method, wherein hybridizing at least one first primer to said first template and at least one second primer to said second template further comprises hybridizing at least one additional primer to said second template (Figure 1).

With regards to claim 17, Kambara teaches a method, wherein said additional primer is selected to hybridize at least in close proximity to a relative short stretch of identical nucleotides on said second template (p. 5, col. 2, paragraphs 66-68, as an example where primers 2 or 3 would bind sequence 1 in close proximity in the 5' direction to multiple instances of GG and CCC; where 'short stretch of identical nucleotides is interpreted to mean 2 or more nucleotides of the same type, e.g. CC, AA, TT, GG).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the technique of differential display taught by Wilkinson to incorporate the modified pyrophosphate sequencing technique taught by Kambara. As taught by Kambara, "the process of the invention has achieved four to five orders of magnitude of high sensitivity" and therefore "only several hundred copies

of DNA are enough for detection." As an added benefit of the technique taught by Kambara, the method is carried out in a reaction vessel with multiple reaction cells, which makes it possible to examine multiple test sites simultaneously (paragraph 13). The benefit of simultaneous analysis of multiple test sites and high sensitivity with small amounts of nucleic acid necessary for each analysis would be obvious to one of ordinary skill in the art who would therefore be motivated to apply the modified pyrophosphate sequencing technique to the differential display analysis taught by Wilkinson with a reasonable expectation of success.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie K. Mummert whose telephone number is 571-272-8503. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0872. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephanie Mummert

Stephanie K. Mummert
Patent Examiner
Art Unit 1637

Cynthia Wilder

CYNTHIA WILDER
PATENT EXAMINER

8/20/2005